UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,443	08/14/2001	Jack Price	GJE-74	9647

23557 7590 07/28/2005

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,443	PRICE, JACK	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/4/5*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

500

DETAILED ACTION

Claims 21-45 are pending in the application.

This Office Action is in response to the Amendment filed on 5/4/05.

Response to Amendment

The rejection of claims 1-6, 10-13, 15-20 under 35 U.S.C. 112 1st paragraph is moot in light of Applicant's cancellation of the claims.

Claims 22, 31-45 are rejected under 35 U.S.C. 112 1st paragraph for reasons set forth of the record mailed on 11/2/04 (as applied to claims 1-6, 10-13, 15-20) and further discussed below.

Claims 21, 23-30 are rejected under 35 U.S.C.102 (b) for reasons discussed below.

Claim 45 is objected to for reasons given below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 and 31-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to this rejection, Applicant argues that the claims are reasonable enabled by the instant specification. First, Applicant asserts that claims drawn to conditionally immortal hematopoietic stem cells and composition comprising said cells are useful *in vitro* or *in vivo* for

many of the same purpose as other HSC, such as being expanded for differentiation, wherein the differentiated cells may be used as a source of various blood cell types or hematopoietic protein, and HSC can also be used to treat patients with cancers and disorders or the blood and immune system. Applicants further assert that Jat et al., 5,688,692 and WO 97/10329 describes conditional immortality and a suitable immortalizing gene, thus provide enablement for the claimed inventions. Second, Applicants assert that the method of treating a cognitive deficit associated with brain damage by intracerebrally administering an effective amount hematopoietic stem cells to a patient to improve cognitive function is reasonable enabled because HSC and their progeny express phenotypic markers and/or have functional properties similar to neural stem cells and differentiated neural cells, wherein the therapeutic benefits of said cells are reported in scientific literature. Applicant indicates (cited Daadi and Weiss) that the transplanted murine HSC were demonstrated to survive two weeks and expresses proteins such as MAP-2, NeuN, NeuroD, TH, GABA and GFAP in a mouse model of stroke, wherein some of the proteins are markers of neural cells and are intrinsically beneficial (such as TH, GABA). Applicant further asserts that neuronal disorder such as Parkinson's disease and Alzheimer's disease would be beneficial from such treatment. Moreover, Applicant cites Koshizuka et al., Priller et al. (I and II), Hess et al., and Goolsby et al. to demonstrate that HSC and their progeny express phenotypic markers and/or have functional properties consistent with neural stem cells and differentiated neural cells. Furthermore, Applicant asserts that human HSC have a neural potential similar to murine HSC. Applicant cites Weimann et al. and asserts that human bone marrow cells have the capability of forming effective neural cells in human adult brains, whereas Hao et al. teach human HSC can express neural progenitor cell markers in vitro and subsequently

differentiate into astrocytes based on morphology and marker expression. Applicant also asserts that Cogle et al. demonstrate that transplanted human bone marrow-derived HSC can differentiate into neurons, astrocytes, and microglia in a long-term setting and states "transplantable human HSC could serve as a therapeutic source for long-term regenerative neuropoiesis." Applicant asserts that the publications confirm the accuracy and sufficiency of the disclosure although some of them are post filing. Furthermore, Applicant asserts that application is not required to show a cure of the disease condition or clinical efficacy is achieved. Applicant thus concludes that every issue raised by the examiner has been addressed, and the office should not doubt the objective truth of the statements according to *In re Marzocchi*. Therefore, the rejection should be withdrawn.

The above arguments have been fully considered but deemed unpersuasive. The reasons for the non-enablement of the instant claims are discussed in detail in the previous office action mailed on 11/2/04. Newly presented claim 22 is drawn to an isolated conditionally immortal human hematopoietic stem cell (HSC). As discussed in the previous office action, the statue of 112 1st paragraph requires the claimed invention is described sufficiently so that one skilled in the art would be able to make and use the claimed invention without undue experimentation. A review of the instant specification reveals that the teaching with regard to conditional immortalization of the HSC is very limited. The specification only discloses making said conditionally immortal HSC by transduce the cells with an oncogene. While the cited WO 92/11355 and WO 93/18137 describe methods of culturing HSC and transform said HSC *in vitro*, they do not demonstrate a clonal HSC cell line that is immortalized. US 5,958,767 discloses methods of culturing and genetic modification of human neural stem cells rather than

conditionally immortalization of HSC. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance of making and using the claimed invention. The prior art teaches that *in vitro* long-term bone marrow culture (LTBMC) systems have a limited life span, and they eventually lose LTBMC-IC. This is still a problem at the time of filing (see page 45, NIH report "stem cell research and future directions"). Although oncogenes such as SV40 large T antigen is well known in the art for immortalizing primary cells into clonal cell lines, whether such application can yield immortalized human HSC is unpredictable due to the problems such as our lack of sufficient knowledge of growth condition of HSC and limited number of true HSC in the source (eg. Cord blood, PB and BM). Jat et al. and US 5,688,592 disclose a method of transducing the SV 40 large T antigen into the genome of a mouse, wherein said mouse can serve as a potential source for immortalized cell lines of various types. However, neither reference has identified conditionally immortalized HSC. Most importantly, this method clearly cannot be applied to human to obtain immortalized HSC. The examiner also fails to recognize the relevance of WO 97/10329 with making an immortalized human HSC because said reference teaches neural transplantation using pluripotent neuroepthelial cells. As such, there is insufficient teaching in both the art and the specification at the time of filing to make a conditionally immortalized human HSC *in vitro*. Without such teaching from the prior art and guidance from the specification, one skilled in the art would have to engage undue experimentation to make the invention as claimed. Therefore, claim 22 is not enabled.

The claimed method of treating cognitive deficit associated with brain damage by intracerebrally administering an effective amount of HSC to a patient is not enabled for same reasons as discussed in the previous office action. With regard to Applicant's argument with

regard to scientific literature, Applicant is again reminded that a therapeutic effect need to be demonstrated since the claims are drawn to a method of treating wherein cognitive function is improved in the patients. However, none of the reference demonstrates this aspect. Chopp et al. demonstrated that murine HSC survive two weeks and express neuronal markers such as MAP-2, NeuroD, TH, GABA and GFAP, wherein some of the markers are involved in certain disease such as Parkinson's and Alzheimer's disease. However, neither reference demonstrate that expression of said marker in cells derived from HSC renders improved cognitive function in a murine Parkinson's and/or Alzheimer's model. Further, Applicant is reminded that mere expression of certain neuronal markers does not mean that the cell has neuronal function. Further research is clearly required to establish such cells actually have neuronal function. Similarly, the post filing art (Priller et al., Hess et al., Goolsby et al., Weimann et al., Hao et al., and Gogle et al) cited by Applicant also fails to demonstrate a therapeutic improvement of cognitive function in a patient except Koshizuka et al. Koshizuka et al. demonstrate recovery of hind limb motor function in mice administered with HSCs from bone marrow after spinal cord injury, whereas the claims are drawn to intracerebral administering HSC to treat cognitive deficit associated with damaged brain. When relying on the post filing reference to provide enablement to the claimed invention, the post filing art should follow exactly the teaching of the specification and reach the expected results as taught by the specification. In the instant case, what's done by Koshizuka et al. is different from the teaching of the specification, wherein the results is improved motor function, not cognitive function as claimed. Furthermore, Koshizuka discloses that transplanted HSCs do not express specific markers for neurons (see abstract, and page 68,

2nd col., 1st paragraph). As such, this reference does not provide support for the enablement of the claimed method.

Moreover, Priller II, the review article provided by Applicant which discuss the therapeutic potential of bone marrow derived cells, clearly provides evidence that treating cognitive deficit using HSC is unpredictable even at 5 years post filing. Priller states "the apparent plasticity of BM stem cells has raised hopes for their use in cell-based repair strategies in the CNS...While the clinical potential of BM stem cell therapy is apparent, there is much to be learnt about the basic biology of stem cell plasticity before we can fully acknowledge the value of bone marrow stem cells in the brain." As such, whether treating cognitive deficit associated with brain damage by HSC is still unpredictable at present.

Although the examiner does not doubt the objective truth of the instant specification and Applicant's arguments, the prior art cited by Applicant and the teaching of the specification is insufficient to support the enablement of the claimed method of treating cognitive deficit for reasons given above. The examiner is not requesting evidence for a cure of the diseased condition, but rather evidence to demonstrate a therapeutic effect of improved cognitive function. In view of limited teaching from the specification and unpredictability from the prior art, one skilled in the art would have to engage in undue experimentation to practice the method as claimed. Therefore, this rejection is maintained.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 23-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakatsuji et al (Cell Structure and Function, 1996, Vol, 21, No.6, pp.624).

The claims are drawn to a conditionally immortalized HSC and a composition comprises said HSC, wherein the claims are further drawn to such HSC wherein the conditional immortality is conferred by an oncogene such as temperature sensitive SV40 T antigen.

Nakatsuji et al. disclose isolation and cloning of conditionally immortalized HSC in mice transformed with SV 40 tsA58 T gene. Nakatsuji et al. disclose that cell lines are established (see entire document). Therefore, Nakatsuji et al. disclose the instantly claimed invention.

Claim Objections

Claim 45 is objected to as being dependent upon a cancelled base claim (1). However, for the purpose of examination, the limitations of claim 1 will be read into claim 45. Applicant is advised to rewrite the claim in independent form including all of the limitations of (canceled) base claim (1).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER